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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
08/817,704	08/25/97	SWAAK	A	P8214-7002

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EXAMINER	
CUNNINGHAM,T	

ART UNIT	PAPER NUMBER
1644	9

DATE MAILED: 12/21/98

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

PTO-90C (Rev. 2/95)
*U.S. GPO: 1996-404-496/40510

Office Action Summary	Application No. 08/817,704	Applicant(s) Swaak, A. J.
	Examiner Thomas Cunningham	Group Art Unit 1644

☐ Responsive to communication(s) filed on 9/30/98.

☑ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *14-29* is/are pending in the application.

Of the above, claim(s) ______ is/are withdrawn from consideration.

☐ Claim(s) ______ is/are allowed.

☐ Claim(s) ______ is/are rejected.

☐ Claim(s) ______ is/are objected to.

☒ Claims *14-29* are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on ______ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on ______ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) ______ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: ______ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). ______

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

1. Claims 14-29 are active. The claims designated 15-30 in the last amendment have been renumbered under Rule 126 as claims 14-29. This is because the preliminary amendment dated 5/5/97 added claims 10 and 12-14 and claim 11 was missing.

2. (Moot) The prior rejection of claims 1-14 under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter is moot in view of cancellation of these claims.

3. The Abstract submitted in the last amendment has been entered.

4. (Moot) The prior rejection of claims 1 and 7 under 35 U.S.C. 112, second paragraph as failing to particularly point out and distinctly claim the invention is moot. In claims like claim 1 and 7 it is unclear what the scope of the term "erythropoietin-like activity" is. Does this term limit the claim to a particular functional activity, or is it nonlimiting in that any activity, e.g. presence of a crossreactive epitope, is encompassed?

--These claims have been canceled and the term in question does not appear in the present claims.

5. Claims 14-29 are rejected under 35 U.S.C. 112, first paragraph as lacking adequate enablement. Claims 14-29 are directed to methods of treating chronic inflammation, and autoimmune diseases such as arthritis using erythropoietin or erythropoietin fragments, derivatives or mutants.

A. <u>Autoimmune diseases, scope</u>. One with skill in the art would not expect to be able to use

erythropoietin products to treat inflammatory or autoimmune diseases in general. Erythropoietin is a humoral regulator of erythropoiesis and stimulates the production of erythrocytes. It is used to treat diseases associated with anemia in order to increase the production of red blood cells. Pages 4-5 of the specification speculate that erythropoietin may exert anti-inflammatory effects either by mobilizing iron to hemoglobin production and away production of hydroxy-radicals associated with tissue damage in diseases like arthritis. Another suggested mechanism is the role EPO may have on Th1/Th2 balance and on particular cytokines.

The study described in the specification indicates that EPO treatment of subjects with chronic anemia associated with rheumatoid arthritis (ACD) resulted in certain clinical improvements, including reductions in pain score and morning stiffness and improvement in well-being.

One with skill in the art would not have had a reasonable expectation of treating diseases other than ACD (or RA) using EPO because of the complexity of the physiological mechanisms of different autoimmune diseases. Phenomena such as abnormal iron or cytokine levels associated with ACD would not reasonably be expected to occur in other autoimmune or inflammatory diseases. Robbins, Pathological Basis of Disease, page 190 indicated that "Although it would be attractive to explain all autoimmune diseases by a single mechanism, it is now clear there are a number of ways by which tolerance can be bypassed" and defects associated with autoimmune diseases differ from one disorder to another. Therefore, it would have been unpredictable whether treatment of subjects having other autoimmune or inflammatory disorders with EPO

would result in clinical improvement.

B. Fragments, derivatives, mutants. One with skill in the art would not be able to identify without undue experimentation erythropoietin fragments or variants without some indication of the desired functional activity (e.g. scavenging iron, modulating cytokine levels, etc) and some indication of conserved structure. It would be necessary to determine all the known and unknown functional activities of erythropoietin and then to determine which compounds had similar activities. According to Smilek et al., PNAS even minor changes in the structure of a biologically active molecule can have drastic effects on functional activity. It would require undue experimentation to determine which erythropoietin derivatives or mutants would retain the desired functional activities. Applicant's attention is directed to Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016 (CAFC 1991):

> Patent applicant is entitled to claim invention generically, if invention is described sufficiently to meet requirements of 35 USC 112; however, applicant, in claims for DNA sequences encoding erythropoietin, which has claimed every possible analog of gene containing about 4,000 nucleotides, but which has provided details for preparing only few EPO analog genes has not provided sufficient disclosure to support its claims, since, in view of structural complexity of EPO gene, manifold possibilities for change in its structure, and uncertainty as to what utility will be possessed by these analogs, additional disclosure is needed as to identifying various analogs within scope of claim, methods for making them, and structural requirements for producing compounds with EPO-like activity.

Why Amgen addresses the unpredictability of which DNA sequences would encode functional erythropoietin analogs, the same or similar issues of unpredictability of the functional

characteristics of analogs of erythropoietin are pertain to whether the claims in the instant application are enabled. Applicant urges on page 6 of the last response that so long as the recited erythropoietin products meet two criteria--that they are nonimmunogenic and ameliorate inflammation--they may be used in the present invention. However, the specification provides no guidance as to which of billions of different possible analogs or fragments would meet these two criteria.

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 14-29 are rejected under 35 U.S.C. 102(b) as being anticipated by GB 2 171 304 A (published 28 August 1986). Claims 14-29 all embrace treatment of "the anemia of rheumatoid arthritis" with EPO because the claimed methods encompass administration of the same compound (EPO) for the same purpose: treating a subject with the anemia of RA. The cited document teaches treatment of the anemia of RA using EPO. Performance of the prior art methods would inherently result in the clinical improvements observed by the instant inventors, such as reductions in joint swelling, pain or inflammation.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thomas M. Cunningham, Ph.D, J.D. whose telephone number is (703) 308-3968. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

TC

THOMAS M. CUNNINGHAM
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GROUP 1800